

Exhibit E

Consideration of Sex as a Biological Variable in NIH-funded Research

Notice Number: NOT-OD-15-102

Key Dates

Release Date: June 9, 2015

Related Announcements

[NOT-OD-16-034](#)

[NOT-OD-16-031](#)

[NOT-OD-16-012](#)

[NOT-OD-16-011](#)

[NOT-OD-15-103](#)

Issued by

National Institutes of Health ([NIH](#))

Purpose

The National Institutes of Health (NIH) is committed to improving the health outcomes of men and women through support of rigorous science that advances fundamental knowledge about the nature and behavior of living systems. Sex and gender play a role in how health and disease processes differ across individuals¹, and consideration of these factors in research studies informs the development and testing of preventive and therapeutic interventions in both sexes. This notice focuses on NIH's expectation that scientists will account for the possible role of sex as a biological variable in vertebrate animal and human studies. Clarification of these expectations is reflected in plans by NIH's Office of Extramural Research (OER) to update application instructions and review questions; once approved by the Office of Management and Budget (OMB), these updates will take effect for applications submitted for the January 25, 2016, due date and thereafter. Please refer to [NOT-OD-15-103](#) for further consideration of NIH expectations about enhancing reproducibility through rigor and transparency.

Background

Women now account for roughly half of all participants in NIH-supported clinical research, which is subject to NIH's Policy on the Inclusion of Women in Clinical Research.² However, more often than not, basic and preclinical biomedical research has focused on male animals and cells.³ An over-reliance on male animals and cells may obscure understanding of key sex influences on health processes and outcomes.

Accounting for sex as a biological variable begins with the development of research questions and study design. It also includes data collection and analysis of results, as well as reporting of findings. Consideration of sex may be critical to the interpretation, validation, and generalizability of research findings. Adequate consideration of both sexes in experiments and disaggregation of data by sex allows for sex-based comparisons and may inform clinical interventions. Appropriate analysis and transparent reporting of data by sex may therefore enhance the rigor and applicability of preclinical biomedical research.⁴

NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data, or other relevant considerations must be provided for applications proposing to study only one sex. Investigators are strongly encouraged to discuss these issues with NIH program staff prior to submission of applications. Further information regarding NIH expectations for the consideration of sex as a biological variable is provided at the following website:

http://orwh.od.nih.gov/sexinscience/overview/pdf/NOT-OD-15-102_Guidance.pdf

- 1 Institute of Medicine. 2001. Exploring the Biological Contributions to Human Health: Does Sex Matter?
<https://www.iom.edu/Reports/2001/Exploring-the-Biological-Contributions-to-Human-Health-Does-Sex-Matter.aspx>
- 2 https://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm
- 3 <http://www.nature.com/news/policy-nih-to-balance-sex-in-cell-and-animal-studies-1.15195>
- 4 <http://www.nature.com/news/policy-nih-plans-to-enhance-reproducibility-1.14586>

Inquiries

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